Synthesis of Novel Analgesic Agents II: Pyrazolidines with Nonoxygenated Phenyl Substituents

MILTON J. KORNET[▲] and HENRY S. I. TAN*

Abstract □ Several 3- and 4-phenylpyrazolidines as well as 3-alkyl-3- and 4-alkyl-4-phenylpyrazolidines were synthesized. Most of the compounds were devoid of analgesic activity by the subcutaneous route. 1,2-Diethyl-4-phenylpyrazolidine possessed one-tenth the activity of codeine.

Keyphrases □ Phenylpyrazolidines, nonoxygenated—synthesis, analgesic activity □ Pyrazolidines, nonoxygenated phenyl—synthesis, analgesic activity □ 1,2-Diethyl-4-phenylpyrazolidine—synthesis, analgesic activity □ Analgesic activity—determination, nonoxygenated phenylpyrazolidines □ Structure–activity relationships—nonoxygenated phenylpyrazolidines

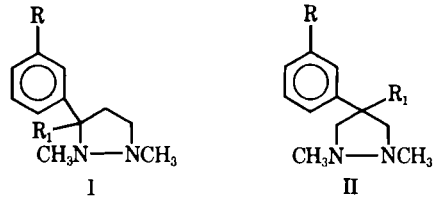
Recently, the preparation and analgesic potency of some 3- and 4-arylpyrazolidines and 3-alkyl-3-aryl- and 4-alkyl-4-arylpyrazolidines of general Structures I and II were reported by this laboratory (1). In these compounds the phenyl ring bears an oxygen function in the *meta*-position. As part of a continuing study of structure–activity relationships in the series, it was decided to prepare compounds having an unsubstituted phenyl ring (I and II, R = H) to determine whether the *meta*-oxygen function is necessary for analgesic activity. These analogs are of interest because a *meta*-oxygen function on the phenyl nucleus is required for analgesic action in the 3-alkyl-3-arylpyrrolidine series (2).

SYNTHESIS

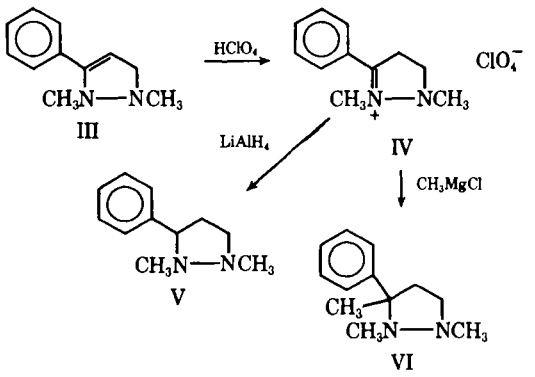
The principal synthetic route for the preparation of compounds having Structure I (R = H) is outlined in Scheme I. The starting material, 1,2-dimethyl-3-phenyl-3-pyrazoline (III), was easily prepared by a one-step Mannich reaction from 1,2-dimethylhydrazine dihydrochloride, formaldehyde, and acetophenone (3). Treatment of III with perchloric acid afforded 1,2-dimethyl-3-phenyl-2-pyrazolinium perchlorate (IV), which served as the key intermediate for the other members of this series.

Reduction of IV with lithium aluminum hydride produced a high yield of 1,2-dimethyl-3-phenylpyrazolidine (V). This compound represents a potential analgesic agent having a central tertiary carbon atom. Previously, V was obtained directly from III by catalytic hydrogenation (3).

Compound IV was reacted with methylmagnesium chloride, and the resulting Grignard complex was decomposed with aqueous ammonium chloride solution. From the neutralized mixture, 1,2,3-trimethyl-3-phenylpyrazolidinium perchlorate was isolated. Treatment of this perchlorate salt with 40% aqueous potassium hydroxide solution afforded the corresponding free base VI. This potential analgesic agent possesses a central quaternary carbon atom.

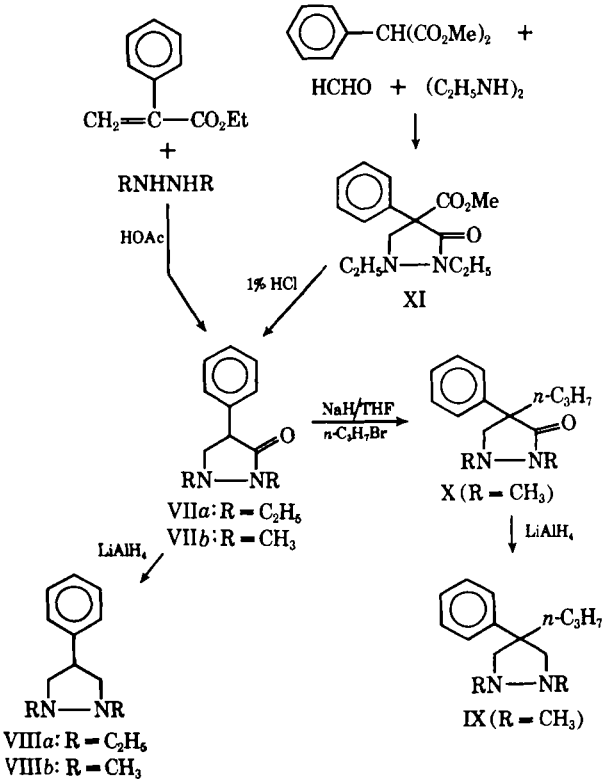


R = OCH_3 or OH
R_1 = H or alkyl



Scheme I

A general route for the preparation of compounds having Structure II (R = H) involved reacting 1,2-dialkylhydrazines with an ethyl α-arylacrylate. By utilizing this procedure (1), 1,2-diethylhydrazine was refluxed with ethyl atropate in glacial acetic acid and afforded 1,2-diethyl-4-phenyl-3-pyrazolidinone (VII*a*) in 54% yield. Similarly, 1,2-dimethyl-4-phenyl-3-pyrazolidinone (VII*b*) was



Scheme II

obtained in 51% yield (Scheme II). These two 3-pyrazolidinones served as the key intermediates for Compound II (R = H).

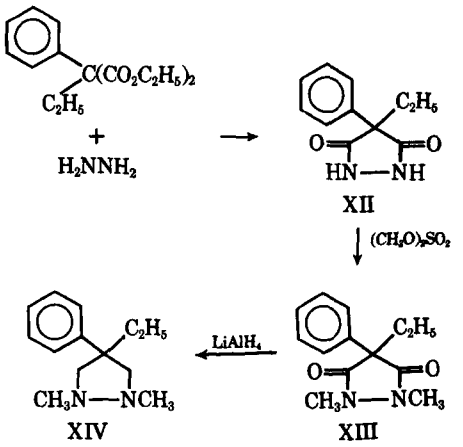
In initial experiments, VII*a* was obtained in 10–15% yields from ethyl atropate and the lithium salt of 1,2-diethylhydrazine, which was generated in turn from *n*-butyllithium and 1,2-diethylhydrazine. The procedure was adapted from the one used by Kaiser *et al.* (4) for the addition of the lithium salts of amines to ethyl atropate. Because of higher yields, the preferred procedure for the preparation of VII involves refluxing 1,2-dialkylhydrazines with an ethyl α-arylacrylate in glacial acetic acid.

Reduction of VII*a* and VII*b* by lithium aluminum hydride afforded the corresponding pyrazolidines VIII*a* and VIII*b*, respectively, in high yield. These compounds represent the potential analgesics of Structure II (R = H) having a central tertiary carbon atom.

The analgesic of Structure II (R = H) having a central quaternary carbon atom, 1,2-dimethyl-4-*n*-propyl-4-phenylpyrazolidine (IX), was prepared in two steps from VII*b*. Alkylation of VII*b* with *n*-propyl bromide and sodium hydride as the base in tetrahydrofuran (THF) yielded 1,2-dimethyl-4-*n*-propyl-4-phenyl-3-pyrazolidinone (X), which gave IX upon reduction by lithium aluminum hydride (Scheme II).

An alternative pathway to the synthesis of compounds of Structure II was briefly explored. Attempts were undertaken to synthesize 1,2-diethyl-4-phenyl-4-carbomethoxy-3-pyrazolidinone (XI) which could be degraded to VII*a*, the key intermediate, by hydrolysis and decarboxylation (5) (Scheme II). A Mannich reaction between 1,2-diethylhydrazine, methyl phenylmalonate, and formaldehyde in methanol with a subsequent cyclization did indeed produce XI. However, due to the low yield (11%) in the latter reaction, the transformation of XI to VII*a* was not investigated.

Another analgesic of Structure II (R = H) having a central quaternary carbon atom, 1,2-dimethyl-4-ethyl-4-phenylpyrazolidine (XIV), was obtained by a different pathway. This compound was prepared in three steps from ethyl ethylphenylmalonate (Scheme III). 4-Ethyl-4-phenylpyrazolidine-3,5-dione (XII) (6, 7) was prepared from ethyl ethylphenylmalonate and 85% aqueous hydrazine hydrate by modifying the procedure of Gillis and Izydore (8). *N*-Methylation with dimethyl sulfate gave 1,2-dimethyl-4-ethyl-4-phenylpyrazolidine-3,5-dione (XIII). Reduction of XIII by lithium aluminum hydride in tetrahydrofuran afforded XIV.



Scheme III

ANALGESIC ACTIVITY

The analgesic activity was determined as previously described (1). The route of administration for all of the compounds was subcutaneous. Compounds V, VI, VIII*b*, IX, and XIV were found to be ineffective at doses up to 100 mg./kg. Compound VIII*a* exhibited an ED_{50} value of 73.3 mg./kg. Two observations are worth noting: (*a*) there are fewer active compounds in the nonoxygenated series than there are in the oxygenated series (1), and (*b*) among the nonoxygenated compounds, VIII*a*, which has some activity, is the only compound with ethyl groups attached to nitrogen. Perhaps larger *N*-substituents would result in compounds of greater activity.

EXPERIMENTAL[1]

1,2-Dimethyl-3-phenyl-3-pyrazoline (III)—This compound was obtained from 13.3 g. (0.1 mole) of 1,2-dimethylhydrazine dihydrochloride, 24.0 g. (0.2 mole) of acetophenone, and 6.0 g. of paraformaldehyde (0.2 mole of HCHO) in 200 ml. of absolute alcohol by the procedure of Hinman *et al.* (3). Distillation gave 4.01 g. (23.0%) of a pale-yellow oil, b.p. 106–108° (9 mm.) [lit. (3) 41% yield, b.p. 83° (2 mm.) and 71° (1.2 mm.)]; IR (film): 6.12 μ (C=C—N); NMR ($CDCl_3$): δ 7.22–7.74 (m, 5, ArH), 5.28 (t, 1, J = 2.5 Hz., vinyl H), 3.86 (d, 2, J = 2.5 Hz., C=CH—CH_2), 2.67 (s, 3, NCH_3), and 2.60 (s, 3, NCH_3).

1,2-Dimethyl-3-phenyl-2-pyrazolinium Perchlorate (IV)—This compound was obtained by dissolving III in ether and neutralizing with a solution of 70% $HClO_4$ in an equal volume of absolute alcohol (9) to Congo red indicator. Recrystallization from absolute alcohol afforded white needles, m.p. 139–143° [lit. (10) m.p. 132–135°].

1,2-Dimethyl-3-phenylpyrazolidine (V)—To a stirred suspension of 1.84 g. (0.049 mole) of lithium aluminum hydride in 50 ml. of tetrahydrofuran was added, in small portions, 3.15 g. (0.0114 mole) of IV over a period of 5 min. After the reaction mixture was refluxed for 18 hr., the complexes were decomposed with 40% aqueous potassium hydroxide solution with ice bath cooling. The tetrahydrofuran was decanted, and the inorganic sludge was extracted three times with 20-ml. portions of tetrahydrofuran. The combined tetrahydrofuran solution was dried, filtered, and concentrated under reduced pressure. The remaining residue was distilled to afford 1.52 g. (76%) of a colorless oil, b.p. 120–122° (17 mm.), $n_D^{24.0}$ 1.5305 [lit. (3) b.p. 72 (1.2 mm.), $n_D^{21.0}$ 1.5318]; IR (film): no absorption at 6.12 μ (C=C—N); NMR ($CDCl_3$): δ 7.23–7.69 (m, 5, ArH) and 1.40–3.95 (m, 11, including the Ar—CH triplet at 3.53 and two NCH_3 singlets at 2.39 and 2.57).

A hydrochloride derivative was prepared and recrystallized from absolute alcohol–ether, m.p. 175–177° (sealed tube).

Anal.—Calc. for $C_{11}H_{17}ClN_2$: C, 62.10; H, 8.07; N, 13.17. Found: C, 62.02; H, 8.09; N, 13.12.

1,2,3-Trimethyl-3-phenylpyrazolidine (VI)—A solution of 12 ml. (0.0348 mole) of 2.85 *M* methylmagnesium chloride in tetrahydrofuran was diluted with 88 ml. of tetrahydrofuran. To the stirred solution of the Grignard reagent was added portionwise 4.80 g. (0.0174 mole) of IV over a period of 3 min. The reaction mixture was refluxed for 18 hr. and decomposed with saturated aqueous ammonium chloride solution. The tetrahydrofuran was decanted, the inorganic sludge was extracted with three 20-ml. portions of tetrahydrofuran, and the combined tetrahydrofuran solutions were dried. After removal of the tetrahydrofuran under reduced pressure, a yellowish-brown solid was obtained; upon recrystallization from absolute alcohol, it gave 1.06 g. of 1,2,3-trimethyl-3-phenylpyrazolidinium perchlorate as white crystals, m.p. 204–207°. From the mother liquor an additional 0.95 g. of the perchlorate was obtained, m.p. 204–206°. The total yield was 39.7%. The free base was obtained by the dropwise addition of 40% aqueous potassium hydroxide solution to 1.76 g. of the perchlorate in 5 ml. of water with trituration until strongly alkaline. The mixture was extracted with three 15-ml. portions of ether. The combined ether solution was dried, filtered, and concentrated under reduced pressure. The remaining residue was distilled and yielded 0.70 g. of a colorless oil, b.p. 114.5° (9 mm.); $n_D^{24.0}$ 1.5300; IR (film): no absorption at 6.12 μ (C=C—N).

Anal.—Calc. for $C_{12}H_{18}N_2$: C, 75.74; H, 9.53; N, 14.72. Found: C, 75.91; H, 9.58; N, 14.82.

Perchlorate.

Anal.—Calc. for $C_{12}H_{19}ClN_2O_4$: C, 49.57; H, 6.57; N, 9.63. Found: C, 49.71; H, 6.66; N, 9.79.

[1] Melting points were determined with a Fisher-Johns apparatus. A Mel-Temp melting-point apparatus was used for melting-point determinations in a sealed tube. All melting points are corrected, whereas boiling points are uncorrected. IR spectra were obtained on a Beckman IR-8 spectrophotometer. NMR spectra were determined on a Varian A-60A spectrometer, using tetramethylsilane as the internal reference for solutions in organic solvents and sodium 2,2-dimethyl-2-silapentane-5-sulfonate (Tiers' salt) for solutions in D_2O. Microanalyses were performed by Dr. Kurt Eder, Geneva, Switzerland. Magnesium sulfate was employed as the drying agent.

A hydrochloride derivative was prepared and recrystallized from isopropyl alcohol–ether, m.p. 208–210° dec. (sealed tube); NMR (D_2O): δ 7.08–7.90 (m, 5, ArH) and 1.46–4.33 (m, 13, including the C—CH_3 singlet at 1.62, the Ar—C—NCH_3 singlet at 2.53, and the NCH_3 singlet at 3.11).

Anal.—Calc. for $C_{12}H_{19}ClN_2$: C, 63.57; H, 8.45; N, 12.35. Found: C, 63.45; H, 8.59; N, 12.43.

Ethyl 3-Phenyl-2-oxosuccinate—This ester was prepared by the method of Levene and Meyer (11). The crude viscous oil obtained from 87.5 g. (0.53 mole) of ethyl phenylacetate, 73.0 g. (0.50 mole) of diethyl oxalate, and 11.5 g. (0.5 g.-atom) of sodium in 250 ml. of absolute alcohol was used directly in the following experiment.

Ethyl Atropate—The crude oxosuccinate obtained was treated with 66 ml. of 40% aqueous formaldehyde solution, 222 ml. of water, and a solution of 54 g. of potassium carbonate in 100 ml. of water as described by Kaiser *et al.* (4). Fractional distillation through a 17.8-cm. (7-in.) column packed with glass helixes gave 56.87 g. (64.6%) of a pale-yellow oil, b.p. 79–82° (1.5 mm.) [lit. (4) yield 58%, b.p. 88–91° (2.5 mm.)]; IR (film): 5.81 μ (ester C=O); NMR ($CDCl_3$): δ 7.31–7.78 (m, 5, ArH), 6.42 (d, 1, C=CH_2), 5.96 (d, 1, C=CH_2), 4.35 (q, 2, OCH_2), and 1.32 (t, 3, C—CH_3). The compound was preserved by refrigerator storage under nitrogen in the presence of hydroquinone methyl ether.

1,2-Diethyl-4-phenyl-3-pyrazolidinone (VII*a*)—*Method A*—To a solution of 4.4 g. (0.05 mole) of 1,2-diethylhydrazine in 100 ml. of anhydrous ether was added 34.5 ml. (0.055 mole) of 1.6 *M* *n*-butyllithium in hexane with stirring at room temperature. Gas evolution was observed. After the solution was stirred for 15 min., a solution of 8.8 g. (0.05 mole) of ethyl atropate in 50 ml. of anhydrous ether was added dropwise over a period of 30 min. The clear yellow solution was stirred for 5 hr. at room temperature and treated with 100 ml. of 3 *N* HCl. The ether layer was separated, and the aqueous phase was extracted with three 50-ml. portions of ether. The aqueous phase was saturated with solid $NaHCO_3$ and extracted three times with 50-ml. portions of ether. The combined ether solution was dried, filtered, and concentrated under reduced pressure. The residue was distilled and afforded 1.06 g. (10%) of a pale-yellow oil, b.p. 121–128° (0.12 mm.). This oil was identical (IR and NMR) to the compound described in *Method C*.

Method B—To a solution of 4.4 g. (0.05 mole) of 1,2-diethylhydrazine in 100 ml. of anhydrous ether was added 78.5 ml. (0.125 mole) of 1.6 *M* *n*-butyllithium in hexane with stirring at room temperature. After the solution was stirred for 15 min., 8.8 g. (0.05 mole) of ethyl atropate in 50 ml. of anhydrous ether was added. The mixture was stirred at room temperature for 20 hr., refluxed for 24 hr., and cooled. After the dropwise addition of 125 ml. of 3 *N* HCl, the mixture was worked up as described in *Method A*. Distillation afforded 1.59 g. (14.6%) of a pale-yellow oil, b.p. 122–125° (0.20 mm.), which was identical (IR and NMR) to the compound described in *Method C*.

Method C—A solution of 8.8 g. (0.05 mole) of ethyl atropate in 10 ml. of glacial acetic acid was added dropwise to an ice-cooled solution of 4.4 g. (0.05 mole) of 1,2-diethylhydrazine in 45 ml. of glacial acetic acid with stirring under a nitrogen atmosphere. After completion of the addition, the solution was refluxed for 17 hr. The acetic acid was removed under reduced pressure, and the residue was dissolved in 20 ml. of water. After the solution was made alkaline by the addition of solid $NaHCO_3$ and saturated with NaCl, the mixture was extracted three times with 25-ml. portions of ether. The combined ether solution was dried, filtered, and evaporated under reduced pressure. Distillation of the remaining oil afforded 5.86 g. (53.8%) of a colorless oil, b.p. 120–127° (0.35 mm.). An analytical sample was obtained from redistilled material, b.p. 116–117° (0.15 mm.); $n_D^{25.8}$ 1.5320; IR (film): 5.97 μ (amide C=O); NMR ($CDCl_3$): δ 7.33 (s, 5, ArH), 2.65–4.23 (m, 7, NCH_2 and aliphatic ring H), 1.22 (t, 3, CO—N—C—CH_3), and 1.13 (t, 3, CH_2N—C—CH_3).

Anal.—Calc. for $C_{13}H_{18}N_2O$: C, 71.53; H, 8.31; N, 12.83. Found: C, 71.28; H, 8.41; N, 12.82.

1,2-Dimethyl-4-phenyl-3-pyrazolidinone (VII*b*)—A solution of 30.0 g. (0.17 mole) of ethyl atropate in 30 ml. of glacial acetic acid was added dropwise to an ice-cooled solution of 10.2 g. (0.17 mole) of 1,2-dimethylhydrazine in 120 ml. of glacial acetic acid with stirring under a nitrogen atmosphere. The solution was refluxed for 19 hr. and worked up as described for VII*a* (*Method C*). Distillation afforded 16.35 g. (50.7%) of a colorless oil, b.p. 115° (0.23 mm.); $n_D^{23.2}$ 1.5529; IR (film): 5.94 μ (amide C=O); NMR ($CDCl_3$): δ 7.34 (s, 5, ArH), 2.95–4.31 (m, 6, including the CO—NCH_3 singlet at 3.06), and 2.66 (s, 3, CH_2—C—NCH_3). The oil solidified upon standing overnight. Recrystallization from ligroin afforded white needles, m.p. 64–65°.

Anal.—Calc. for $C_{11}H_{14}N_2O$: C, 69.45; H, 7.42; N, 14.72. Found: C, 69.57; H, 7.51; N, 14.65.

1,2-Diethyl-4-phenylpyrazolidine (VIII*a*)—A solution of 4.04 g. (0.0185 mole) of VII*a* in 10 ml. of anhydrous ether was added dropwise to a stirred suspension of 0.70 g. (0.0185 mole) of lithium aluminum hydride in 20 ml. of anhydrous ether. After completion of the addition, the mixture was refluxed for 17 hr. The reaction mixture was cooled in an ice bath and decomposed by the cautious addition of 40% aqueous potassium hydroxide solution. The ether was decanted, the inorganic sludge was extracted three times with 20-ml. portions of ether, and the combined ether solution was dried. After filtration of the solution and removal of the ether under reduced pressure, the remaining residue was distilled to yield 2.82 g. (74.8%) of a colorless oil, b.p. 73–74° (0.10 mm.); $n_D^{26.0}$ 1.5178; IR (film): no absorption at 5.97 μ (amide C=O); NMR ($CDCl_3$): δ 7.33 (s, 5, ArH), 2.14–4.03 (m, 9, including a quartet due to the N$CH_2$$CH_3$ protons at 2.78), and 1.14 (t, 6, C—CH_3).

Anal.—Calc. for $C_{13}H_{20}N_2$: C, 76.42; H, 9.87; N, 13.71. Found: C, 76.61; H, 10.00; N, 13.81.

A picrate derivative was prepared and recrystallized from absolute alcohol, m.p. 99.5–111°.

Anal.—Calc. for $C_{19}H_{23}N_5O_7$: C, 52.65; H, 5.35; N, 16.16. Found: C, 53.12; H, 5.07; N, 16.30.

1,2-Dimethyl-4-phenylpyrazolidine (VIII*b*)—A solution of 4.00 g. (0.021 mole) of VII*b* in 10 ml. of anhydrous ether was added dropwise to a stirred suspension of 0.80 g. (0.021 mole) of lithium aluminum hydride in 20 ml. of anhydrous ether. The mixture was refluxed for 17 hr. and worked up as described for VIII*a*. Distillation gave 2.79 g. (75.5%) of a colorless oil, b.p. 84° (1.3 mm.); $n_D^{24.0}$ 1.5325; IR (film): no absorption at 5.94 μ (amide C=O); NMR ($CDCl_3$): δ 7.37 (s, 5, ArH) and 2.45–3.98 (m, 11, including a singlet due to the NCH_3 protons at 2.57).

Anal.—Calc. for $C_{11}H_{16}N_2$: C, 74.96; H, 9.15; N, 15.89. Found: C, 74.85; H, 9.18; N, 15.51.

A hydrochloride derivative was prepared and recrystallized from isopropyl alcohol–ether, m.p. 106.5–108°.

Anal.—Calc. for $C_{11}H_{17}ClN_2$: C, 62.10; H, 8.07; Cl, 16.66; N, 13.17. Found: C, 62.08; H, 8.05; Cl, 16.25; N, 12.81.

1,2-Dimethyl-4-*n*-propyl-4-phenyl-3-pyrazolidinone (X)—Sodium hydride (50% mineral oil dispersion, 4.67 g., 0.097 mole) was rapidly weighed, washed three times with hexane and once with tetrahydrofuran, suspended in 145 ml. of tetrahydrofuran, and charged into a reaction flask. To the stirred suspension was added dropwise a solution of 15.4 g. (0.081 mole) of VII*b* in 20 ml. of tetrahydrofuran. After completion of the addition, the reaction mixture was refluxed for 90 min., during which time hydrogen evolution was observed. The mixture was cooled to room temperature, and a solution of 19.93 g. (0.162 mole) of *n*-propyl bromide in 20 ml. of tetrahydrofuran was added dropwise. After the addition was complete, the reaction mixture was refluxed for 17 hr., cooled in an ice bath, and decomposed with saturated aqueous ammonium chloride solution. The tetrahydrofuran was decanted, and the inorganic sludge was extracted with three 25-ml. portions of tetrahydrofuran. The combined tetrahydrofuran solution was evaporated under reduced pressure, and the residue was dissolved in 50 ml. of ether and dried. After removal of the ether under reduced pressure, the remaining residue was distilled and afforded 10.38 g. (55.2%) of a colorless oil, b.p. 120–121° (0.40 mm.); $n_D^{20.7}$ 1.5350; IR (film): 5.95 μ (amide C=O); NMR ($CDCl_3$): δ 7.18–7.72 (m, 5, ArH), 3.58 (d, 1, aliphatic ring H), 3.32 (d, 1, aliphatic ring H), 3.00 (s, 3, CO—NCH_3), 2.51 (s, 3, CH_2NCH_3), and 0.57–2.11 (m, 7, *n*-propyl H).

Anal.—Calc. for $C_{14}H_{20}N_2O$: C, 72.38; H, 8.68; N, 12.06. Found: C, 72.38; H, 8.80; N, 12.04.

1,2-Dimethyl-4-*n*-propyl-4-phenylpyrazolidine (IX)—To a stirred suspension of 1.63 g. (0.043 mole) of lithium aluminum hydride in 50 ml. of anhydrous ether was added dropwise a solution of 9.97 g. (0.043 mole) of X in 10 ml. of anhydrous ether. The reaction mixture was refluxed for 18 hr. and worked up as described for VIII*a*. Distillation afforded 7.51 g. (80.2%) of a colorless oil, b.p. 82–83° (0.16 mm.). The oil became cloudy after standing overnight. Redistillation gave a clear product, b.p. 75–77° (0.15 mm.); $n_D^{26.8}$ 1.5174; IR (film): no absorption at 5.95 μ (amide C=O); NMR

($CDCl_3$); δ 7.30 (s, 5, ArH), 3.29 (d, 2, aliphatic ring H), 3.01 (d, 2, aliphatic ring H), 2.50 (s, 6, NCH_3), and 0.60–2.22 (m, 7, *n*-propyl H).

Anal.—Calc. for $C_{14}H_{22}N_2$: C, 77.01; H, 10.16; N, 12.83. Found: C, 77.01; H, 10.06; N, 12.78.

A bisulfate derivative was prepared by the dropwise addition of concentrated H_2SO_4 to a solution of the compound in ether to a pH of 4–5 with ice cooling. The solvent was removed under reduced pressure. The viscous residue solidified upon trituration with ether. Recrystallization of the solid from isopropyl alcohol–ether yielded a white powder, m.p. 102.5–104°.

Anal.—Calc. for $C_{14}H_{24}N_2O_4S$: C, 53.14; H, 7.64; N, 8.85. Found: C, 53.33; H, 7.73; N, 8.85.

4-Ethyl-4-phenylpyrazolidine-3,5-dione (XII)—A mixture of 52.86 g. (0.20 mole) of ethyl ethylphenylmalonate and 141.5 g. (2.40 moles) of an aqueous solution of hydrazine hydrate was refluxed for 6 days. The mixture was distilled at atmospheric pressure, where a low boiling liquid (b.p. 81–125°) was collected. Further evaporation of the residue at reduced pressure afforded a glasslike solid, about m.p. 45°. The solid was dissolved in water, and upon acidification with 10% aqueous HCl, 23.7 g. (58%) of a white crystalline material was obtained, m.p. 197–198.5° [lit. m.p. 196–197° (10) and 198° (11)]; IR (KBr): 5.80 and 6.02 μ (amide C=O); NMR (dimethyl sulfoxide-d_6): δ 7.41 (m, 5, ArH), 2.04 (q, 2, CH_2), and 0.88 (t, 3, CH_3).

1,2-Dimethyl-4-ethyl-4-phenylpyrazolidine-3,5-dione (XIII)—A mixture of 6.12 g. (0.03 mole) of XII and 12 ml. (about 0.09 mole) of dimethyl sulfate was heated at 145° for 4 hr. The dark mixture was cooled, and 6 ml. of H_2O was added. The mixture was carefully saturated with solid K_2CO_3 and extracted with three 25-ml. portions of $CHCl_3$. The combined $CHCl_3$ solution was dried, filtered, and concentrated under reduced pressure. Distillation of the remaining residue afforded 4.90 g. (70.4%) of a pale-yellow viscous oil, b.p. 126–126.5° (0.08 mm.); $n_D^{25.9}$ 1.5438; IR (film): 5.75 and 5.92 μ (amide C=O); NMR ($CDCl_3$); δ 7.10–7.78 (m, 5, ArH), 3.22 (s, 6, NCH_3), 2.19 (q, 2, CH_2), and 0.90 (t, 3, C—CH_3). The oil solidified upon standing, m.p. 41.5–45°. Recrystallization from ligroin (b.p. 66–75°) with charcoal treatment afforded white crystals, m.p. 77–79°.

Anal.—Calc. for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.40; H, 6.94; N, 12.05.

1,2-Dimethyl-4-ethyl-4-phenylpyrazolidine (XIV)—To a stirred suspension of 1.30 g. (0.034 mole) of lithium aluminum hydride in 35 ml. of tetrahydrofuran was added dropwise a solution of 5.34 g. (0.023 mole) of XIII in 15 ml. of tetrahydrofuran. The mixture was refluxed for 24 hr. and worked up as described for VIII*a*. Distillation produced 2.84 g. (60.6%) of a colorless oil, b.p. 69.5–70° (0.10 mm.); $n_D^{25.7}$ 1.5237; IR (film): no absorption at 5.75 and 5.92 μ (amide C=O); NMR ($CDCl_3$); δ 7.24 (s, 5, ArH), 3.25 (d, 2, aliphatic ring H), 2.98 (d, 2, aliphatic ring H), 2.49 (s, 6, NCH_3), 1.89 (q, 2, CH_2—CH_3), and 0.68 (t, 3, C—CH_3).

Anal.—Calc. for $C_{13}H_{20}N_2$: C, 76.42; H, 9.87; N, 13.71. Found: C, 76.32; H, 9.81; N, 13.62.

A hydrochloride derivative was prepared. Recrystallization from isopropyl alcohol–hexane afforded colorless needles, m.p. 146.5–148°.

Anal.—Calc. for $C_{13}H_{21}ClN_2$: C, 64.85; H, 8.79; N, 11.63. Found: C, 64.91; H, 8.88; N, 11.65.

1,2-Diethyl-4-phenyl-4-carbomethoxy-3-pyrazolidinone (XI)—A mixture of 1.76 g. (0.02 mole) of 1,2-diethylhydrazine, 0.7 g. of paraformaldehyde (0.023 mole of HCHO), and 5.2 g. (0.025 mole) of methyl phenylmalonate in 20 ml. of methanol was refluxed for 24 hr. under a nitrogen atmosphere. The solvent was removed under reduced pressure, and the granulelike residue was distilled to afford 4.05 g. (85.5% recovery) of methyl phenylmalonate (identified by IR) and 0.63 g. (11.4%) of a yellow viscous oil, b.p. 137–139° (0.28 mm.). Redistillation of the latter oil gave a light-yellow oil, b.p. 124–125° (0.10 mm.); $n_D^{25.9}$ 1.5160; IR (film): 5.76 (ester C=O) and 5.91 μ (amide C=O).

Anal.—Calc. for $C_{15}H_{20}N_2O_3$: C, 65.20; H, 7.30; N, 10.14. Found: C, 64.97; H, 7.63; N, 10.18.

REFERENCES

(1) M. J. Kornet and H. S. I. Tan, *J. Pharm. Sci.*, **61**, 188(1972).

(2) J. F. Cavalla, R. Jones, M. Welford, J. Wax, and C. V. Winder, *J. Med. Chem.*, **7**, 412(1964).

(3) R. L. Hinman, R. D. Ellefson, and R. D. Campbell, *J. Amer. Chem. Soc.*, **82**, 3988(1960).

(4) E. M. Kaiser, C. L. Mao, C. F. Hauser, and C. R. Hauser, *J. Org. Chem.*, **35**, 410(1970).

(5) H. Stamm, *Arch. Pharm.*, **302**, 253(1969).

(6) A. W. Dox, *J. Amer. Chem. Soc.*, **54**, 3674(1932).

(7) H. Ruhkopf, *Ber.*, **73B**, 820(1940).

(8) B. T. Gillis and R. A. Izydore, *J. Org. Chem.*, **34**, 3181(1969).

(9) N. J. Leonard, A. S. Hay, R. W. Fulmer, and V. W. Gash, *J. Amer. Chem. Soc.*, **77**, 439(1955)

(10) J.-L. Aubagnac, J. Elguero, and R. Jacquier, *Bull. Soc. Chim. Fr.*, **1967**, 3516.

(11) P. A. Levene and G. M. Meyer, "Organic Syntheses," coll. vol. II, Wiley, New York, N. Y., 1943, p. 288.

ACKNOWLEDGMENTS AND ADDRESSES

Received July 6, 1971, from the *Department of Pharmaceutical Chemistry, College of Pharmacy, University of Kentucky, Lexington, KY 40506*

Accepted for publication November 1, 1971.

Abstracted in part from a dissertation submitted by H. S. I. Tan to the Graduate School, University of Kentucky, in partial fulfillment of the Doctor of Philosophy degree requirements.

The authors are grateful to Dr. L. J. Sargent, National Institutes of Health, for the analgesic data.

* Present address: College of Pharmacy, University of Cincinnati, Cincinnati, OH 45221

▲ To whom inquiries should be directed.